In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Case No. 11-138V

August 29, 2016

DAVID JEWELL and WANDA JEWELL, parents of L.J., deceased,	*	**TO BE PUBLISHED**
Petitioners,	*	Special Master Hamilton-Fieldman
v.	*	Entitlement; Causation-in-fact; Hepatitis B ("Hep B") vaccine; Inactivated Polio vaccine ("IPV"); Diphtheria-Tetanus-acellular-Pertussis ("DTaP") vaccine; haemophilus influenzae type B ("HiB") vaccine; pneumococcal conjugate ("PCV") vaccine; Rotavirus vaccine; Sudden Infant Death Syndrome ("SIDS").
SECRETARY OF HEALTH AND HUMAN SERVICES ,	*	
Respondent.	*	

Ronald Homer, Conway, Homer & Chin-Caplan, P.C., Boston, MA, for Petitioner.
Glenn MacLeod, United States Department of Justice, Washington, DC, for Respondent.

DECISION ON ENTITLEMENT[1]

On March 7, 2011, David and Wanda Jewell ("Petitioners") filed a petition on behalf of their deceased daughter, L.J., under the National Vaccine Injury Compensation Program[2] (hereinafter "the Program"). According to the amended petition filed by Petitioners on April 3, 2012, the administration of hepatitis B ("Hep B"), inactivated polio ("IPV"), Diptheria-Tetanus-

[1] Because this Published Decision contains an explanation for the undersigned's action in this case, she intends to post this document on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (2012). Therefore, as provided by Vaccine Rule 18(b), each party has 14 days within which to request redaction "of any information furnished by that party (1) that is trade secret or commercial or financial information and is privileged or confidential, or (2) that are medical files and similar files the disclosure of which would constitute a clearly unwarranted invasion of privacy." Otherwise, this entire document will be available to the public. *Id.*

[2] The applicable statutory provisions defining the Program are found at 42 U.S.C. § 300aa-10 *et seq.* (2012).

acellular-Pertussis ("DTaP"), haemophilus influenzae type B ("HiB"), pneumococcal conjugate ("PCV"), and rotavirus vaccines on April 8, 2009 caused L.J.'s death. Am. Pet., April 3, 2012, at 1. For the reasons set forth below, the undersigned concludes that Petitioners are not entitled to an award.

I. FACTS

L.J. was born on February 7, 2009 at 40 weeks gestational age, the product of an uncomplicated pregnancy.[3] Pet. Ex. 1 at 114; Pet. Ex. 3 at 4, 13. At birth, her APGAR scores were 9 and 9. Pet. Ex. 1 at 114. She was administered her first Hep B vaccination the day after her birth, Pet. Ex. 4 at 33, and was noted to have had normal growth and development during her first few months of life.

L.J. was seen by her pediatrician, Dr. Keith Boykin, on February 9, 2009 and February 27, 2009. Pet. Ex. 4 at 11-14, 20-22. At her two-day visit on February 9th, Mrs. Jewell reported that L.J. slept on her back; at her 20-day visit, L.J. slept on her "back and side." *Id*. at 12, 21. At both visits, L.J. was noted to have had good health and normal behavior. *Id*. at 8, 12-13, 21-22; Pet. Ex. 9 at 1.

On April 8, 2009, at her two-month well-child check-up, L.J. was administered her second dose of the Hep B vaccine and her first doses of the DTaP, IPV, HiB, PCV, and RV vaccines. Pet. Ex. 4 at 4, 7-9; Pet. Ex. 5 at 1. The vaccines were administered at approximately 1:50 p.m. Pet. Ex. 4 at 6; Pet. Ex. 7 at 6. During the visit, L.J.'s pediatrician again noted that she was healthy and behaving normally. Pet. Ex. 7 at 7-8; *see also* Pet. Ex. 7 at 4 (L.J.'s pediatrician reporting to law enforcement after her death that she "had never been sick, and she was a healthy baby.").

L.J.'s medical records are ambiguous regarding the nature and extent of her symptoms during the afternoon and evening following vaccination. According to Mr. Jewell's affidavit, "that night, [L.J.] was fussy and did not eat much." Pet. Ex. 9 at 1-2. According to the April 9, 2009 police report that was completed after L.J.'s death, Mr. Jewell told responding officers that L.J. "was fine when they put her to bed," though she was "crying a little more than usual" and "didn't want to take her bottle." Pet. Ex. 7 at 4. Mrs. Jewell reported to the officers that "after the Dr's appt [sic] she and her husband met up and had dinner with [L.J.'s sister, E.J.] and [L.J.]. Lindsey slept after shots and slept through dinner and the car ride home." *Id*. at 7.

[3] Mrs. Jewell and L.J. were noted to have had an Rh incompatibility: Mrs. Jewell was B and RH negative; L.J. was AB and RH positive. Pet. Ex. 4 at 21. L.H. was identified as "Coomb's positive." *Id*.

There is no dispute that L.J. was afebrile and "was fine" when she was put to sleep in to her crib at approximately 9:45 or 10 p.m. on the day of vaccination. Pet. Ex. 7 at 3-4, 7. According to Mrs. Jewell's statements to law enforcement, L.J. "whined and cried a little bit for about 15 minutes however finally went to sleep." Id. at 7. Mrs. Jewell reported that, at bedtime, L.J. "only took 3 oz of formula and was not super cranky but was a little irritable and whimpering." *Id*.[4] At 10 p.m., Mrs. Jewell reported, she heard L.J. breathing and noted that she "seemed to be just fine." *Id*. Mrs. Jewell also reported that L.J. "had started rolling on her side and would end up on her tummy so she put a little body bumper in the crib which kept [L.J.] from rolling over on her tummy." *Id*.

Mrs. Jewell woke up at approximately 10 a.m. the following morning and became concerned that she hadn't heard any noises on L.J.'s baby monitor. Pet. Ex. 7 at 7. She "went into the babies room [sic] and rubbed the top of [L.J.'s] head and saw that she looked purple and she felt like something was wrong." *Id*. "Mrs. Jewell said that [L.J.] felt slightly warm." *Id*. at 7-8. Mrs. Jewell called 911, and responding personnel discovered L.J. "laying on her right side," with both a white swaddle and a pink blanket "wrapped around her." *Id*. at 3. When the responding officers asked Mrs. Jewell whether this was the position that L.J. was in when she came in to the room, Mrs. Jewell responded that "it was," though she had taken L.J. out of the crib to attempt CPR before replacing her, apparently in the same position. *Id*. Mrs. Jewell also stated that she "had the baby in a onesie and swaddled in a blanket that has butterfly type wings that wrap around the baby and she also had a blanket around the baby." *Id*. at 8. L.J. was pronounced Dead On Arrival ("DOA") by Fire and Rescue personnel at 10:15 a.m. *Id*. at 3.

According to the report from an autopsy conducted on April 10, 2009, L.J.'s cause of death was Sudden Infant Death Syndrome. Pet. Ex. 6 at 4-7. There was evidence of pulmonary and thymic petechiae consistent with a pathological SIDS diagnosis, but there was no evidence of "trauma, disease, or congenital anomaly." *Id*. The autopsy revealed petechial hemorrhages under the pleura of each lung and in the thymus, lungs that were congested and slightly heavy (65 g right, 55 g left), and a slightly heavy brain (583 g). *Id*. A toxicology screen, a virology culture, influenza PCR, and antibodies of blood and spinal fluid were negative. *Id*. The autopsy report documented that L.J. had been found by her mother "dead in her crib, on her back, slightly on her right side, in the same position in which she had been placed down to sleep." Pet Ex. 6 at 6.

II. PROCEDURAL HISTORY

Although Petitioners were *pro se* when they filed their original petition, they immediately expressed an interest in retaining counsel. *See* Scheduling Orders filed April 13, 2011; June 23,

[4] The record does not contain an affidavit authored by Mrs. Jewell. All of her statements were reported to responding officers and law enforcement personnel.

2011; July 19, 2011. On August 8, 2011, Ronald Homer filed a consented motion to substitute himself as attorney of record. Petitioners filed eight medical record and other exhibits on October 3 and 4, 2011, and a statement of completion on December 15, 2011. *See* Pet. Exs. 1-8.

On February 22, 2012, Respondent filed a Rule 4(c) Report in which she argued that Petitioners are not entitled to compensation for L.J.'s allegedly vaccine-caused death because they had not presented any evidence of a Vaccine Table injury, and because they had failed to articulate a causal theory by which the administered vaccines had caused her death. Resp. Rep. at 5-6. Respondent pointed out that none of L.J.'s treating physicians attributed her death to her vaccinations, and she argued that the cause of L.J.'s death, SIDS, is, by definition, unrelated to vaccination. *Id*. at 6-8.

Petitioners filed an amended petition, as well as an affidavit authored by Mr. Jewell, on April 3, 2012. *See* Pet. Ex. 9.

On November 6, 2012, Petitioners filed an expert report authored by Dr. Douglas Miller, M.D., with referenced medical literature and Dr. Miller's curriculum vitae ("CV"). Pet. Exs. 11 (expert report), 13-35 (medical literature), 12 (CV). On May 17, 2013, Respondent filed expert reports authored by Dr. Lucy B. Rorke-Adams., M.D., and Dr. Christine McCusker, M.D. Pet. Exs. A (Dr. Rorke-Adams' report), B (Dr. Rorke-Adams' CV); C (Dr. McCusker's report), D (Dr. McCusker's CV), E1-E17 (Dr. McCusker's medical literature). Petitioners filed a supplemental expert report authored by Dr. James Oleske on December 11, 2013. Pet. Ex. 36; *see also* Pet. Ex. 37 (Dr. Oleske's CV). Respondent filed a responsive expert report authored by Dr. McCusker on February 10, 2014. *See* Pet. Ex. F.

The undersigned subsequently scheduled an evidentiary hearing on the issue of vaccine causation. Petitioners filed pre-hearing submissions on April 24, 2014; Respondent filed pre-hearing submissions on May 15, 2014 and June 12, 2014. The entitlement hearing was held in Washington, DC on June 26-27, 2014. *See* Transcript of Proceedings ("Tr."). The parties filed simultaneous post-hearing briefs on August 22, 2014. The matter is now ripe for a decision on entitlement.

III. ANALYSIS

A. Standards of Adjudication

To receive compensation under the Vaccine Act, Petitioner must demonstrate either that: (1) she suffered a "Table injury" by receiving a covered vaccine and subsequently developing a listed injury within the time frame prescribed by the Vaccine Injury Table set forth at 42 U.S.C. § 300aa-14, as amended by 42 C.F.R. § 100.3; or (2) that she suffered an "off-Table Injury," one not listed on the Table as a result of her receipt of a covered vaccine. *See* 42 U.S.C. §§ 300aa-11(c)(1)(C); *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006).

Because Petitioner does not allege a Table injury in this case, she must prove that her injury was caused-in-fact by an on-Table vaccine. To establish causation-in-fact, Petitioner must demonstrate by a preponderance of the evidence that the vaccine was the cause of the injury. 42 U.S.C. § 300aa-13(a)(1)(A). Petitioners are required to prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321-22 (Fed. Cir. 2010) (quoting *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)).

In the seminal case of *Althen v. Secretary of the Department of Health and Human Services*, the Federal Circuit set forth a three-pronged test used to determine whether a petitioner has established a causal link between a vaccine and the claimed injury. *See Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278-79 (Fed. Cir. 2005). The *Althen* test requires the petitioners to set forth: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* To establish entitlement to compensation under the Program, a petitioner is required to establish each of the three prongs of *Althen* by a preponderance of the evidence. *See id.*

Specifically, under the first prong of *Althen*, Petitioners must offer a scientific or medical theory that answers in the affirmative the question "can the vaccine(s) at issue cause the type of injury alleged?" *See Pafford v. Sec'y of Health & Human Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004). This may be accomplished in a number of ways. *Id.* "Reliability and plausibility of pathogenesis can be bolstered by providing evidence that at least a sufficient minority in the medical community has accepted the theory, so as to render it credible." *Id.* In addition, epidemiological studies and an expert's experience, while not dispositive, lend significant credence to the claim of reliability; articles published in respected medical journals, which have been subjected to peer review, are also persuasive. *Id.* However, publication "does not necessarily correlate with reliability," because "in some instances well-grounded but innovative theories will not have been published." *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 593–94 (1993).

In addition to showing that the vaccine at issue can cause a particular injury, a petitioner must also prove that the vaccine actually *did* cause the alleged injury in a particular case. *See Pafford*, 2004 WL 1717359, at *4 (emphasis added); *Althen*, 418 F.3d at 1279. A petitioner does not meet this obligation by showing only a temporal association between the vaccination and the injury; the petitioner must explain "how and why the injury occurred." *Pafford*, 2004 WL 1717359, at *4.

While a temporal association alone is insufficient to establish causation under the third prong of *Althen*, a petitioner must show that the timing of the injury fits with the causal theory. *See Althen*, 418 F.3d at 1278. For example, if the petitioner's theory involves a process that

takes several days to develop after vaccination, an injury that occurred within a day of vaccination would not be temporally consistent with that theory. Conversely, if the theory is one that anticipates a rapid development of the reaction post-vaccination, the development of the alleged injury weeks or months post-vaccination would not be consistent with that theory. The special master cannot infer causation from temporal proximity alone. In fact, it has been held, that where a petitioner's expert views the temporal relationship as the "key" indicator of causation, the claim must fail. *See Thibaudeau v. Sec'y of Health & Human Servs.*, 24 Cl. Ct. 400, 403-04 (Fed. Cl. Oct. 23, 1991); *see also Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992); *Hasler v. United States*, 718 F.2d 202, 205 (6th Cir. 1983) (stating that inoculation is not the cause of every event that occurs within a ten-day period following it).

A petitioner who demonstrates by a preponderance of the evidence that he suffered an injury caused by vaccination is entitled to compensation, unless the respondent can demonstrate by a preponderance of the evidence that the injury was caused by factors unrelated to the vaccination. *See Althen*, 418 F.3d at 1278; *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 547 (Fed. Cir. 1994).

B. The Parties' Arguments

a. Petitioners' Arguments

i. Dr. Douglas Miller

1. Qualifications

Dr. Miller received his doctorate in medicine from the University of Miami School of Medicine and completed two residencies in anatomic pathology and neuropathology at the Massachusetts General Hospital and at Harvard Medical School. Pet. Ex. 12; Tr. 395. He also received a PhD in physiology and biophysics, having studied "nerve physiology [and] … mechanisms of synaptic transition between nerves and nerve cells." Tr. 394-95. He has served as a Faculty Fellow at the University of Pennsylvania School of Medicine, Center for Clinical Epidemiology and Biostatistics, and was additionally a Fellow in the Division of Rheumatology. *Id*. He currently teaches at the University of Missouri School of Medicine, works as an attending pathologist at the University, and is an associate medical examiner. Tr. 398.

At hearing, the undersigned admitted Dr. Miller as an expert in neuropathology and anatomic pathology. Tr. 400.

2. Theory

At hearing and in his expert reports, Dr. Miller argued that vaccines are capable of causing SIDS in vulnerable infants, and that such deaths occur in a manner consistent with an established model – called the "Triple Risk Model" – of SIDS risk factors and vulnerabilities. *See* Pet. Ex. 14[5] at 2-3. According to the Triple Risk Model, which was postulated by Dr. Hannah Kinney, infants are particularly susceptible to SIDS when three conditions are met: 1) the infant is in a critical developmental period, i.e., between one and twelve months of life, with peak risk occurring between two and four months; 2) the infant has inherent brainstem abnormalities – also referred to herein as 5-HT system[6] defects, or serotonin defects – which lead to deficiencies in serotonin-mediated synaptic activity; and 3) the infant is subject to an environmental factor, also known as an "exogenous stressor," such as a prone sleeping position, an upper respiratory infection ("URI"), or an excessively warm sleeping environment. Pet. Ex. 11 at 3-4; Tr. 418-20; *Filiano* at 2-3. Dr. Miller theorized that vaccinations, by design, are capable of triggering "systemic cytokine release and cytokine-mediated abnormal brainstem responses," and that this cytokine activity, when "acte[ing] in a brainstem … already deficient in serotonergic drive for respiratory effort, [can] lead[] to an apneic[7] episode from which [the patient] d[oes] not recover, i.e. SIDS." Pet. Ex. 11 at 5.

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[5] Filiano, J., & Kinney, H., *A Perspective on Neuropathologic Findings in Victims of the Sudden Infant Death Syndrome: The Triple-Risk Model*, Biol. Neonate, 1994; 65: 194-97 [hereinafter *Filiano*].

[6] Dr. McCusker described the function of the 5-HT system as "regulat[ion of] sleep and arousal patterns." Tr. 240. She explained that "there is development of this system as you age:" "the sleep system has a maturational component and that … maturity occurs from gestational age, second trimester … through to ten months." *Id*. Dr. Miller testified that 5-HT is a neurotransmitter, and that it is "involved in the sensing of CO2 levels and in stimulating respiratory drive to produce arousal and breathing in the setting of excess CO2 in the bloodstream." Tr. 425-26. 5-HT system defects are present at birth. Tr. 411. Functionally speaking, the 5-HT system is "one of the main components of the human CO2[-]sensing sleep arousal system;" "one of its important functions is to cause arousal and stimulate breathing in a situation where the CO2 levels in the blood rise above some threshold." Tr. 413.

Throughout this decision, the undersigned will use the terms "5-HT system" and "serotonergic system" interchangeably.

[7] "Apnea" or "apneic" refers to "the cessation of breathing." *Dorland's Illustrated Medical Dictionary* (*Dorland's*), 116 (32nd. Ed. 2012).

Dr. Miller, who agreed with L.J.'s medical examiner that her death was attributable to SIDS, noted that L.J.'s autopsy slides "suggest[] the presence of … hypoplasia of the arcuate nuclei,[8]" an abnormality present in many cases of SIDS, consistent with the second condition of Dr. Kinney's Triple Risk Model. Tr. 416, Pet. Ex. 11 at 3-4. Citing Dr. Kinney's studies, Dr. Miller explained that the ventral arcuate nuclei of the medulla, which, as the lowest part of the brainstem, is "responsible for the initiation and regulation of muscle efforts underlying breathing," are defective in many SIDS cases. *Id*. at 3-4; Pet. Ex. 18[9]; Pet. Ex. 20[10] ("[T]he most robust neurochemical abnormality in SIDS involves the medullary 5-HT system [], which is involved in approximately 70% of SIDS deaths"); Tr. 452-54. According to Dr. Miller, "there's a reasonable probability that [L.J.] had a defective arcuate nucleus," and that her death resulted from "failed mechanisms of arousal and inadequate reactions to apneic episodes during sleep." Pet. Ex. 11 at 3-4; Tr. 451. Dr. Miller testified that he had never seen hypoplasia or aplasia of the arcuate nucleus in a non-SIDS case. Tr. 413.

Even if L.J. did not have a defective arcuate nucleus, *see* p. 9, *infra*, Dr. Miller's opinion is that the vaccines she received on April 8, 2009 were a "substantial contributing factor" to her death. Tr. 494. Dr. Miller explained that, because the literature suggests that most SIDS cases are attributable in part to defective 5-HT systems, it is likely that L.J.'s 5-HT system was defective, making her vulnerable to exogenous stressors. 5-HT neurons are designed to increase their firing in response to increased levels of carbon dioxide, which leads to more active breathing and arousal, so that the body doesn't die of apnea. Tr. 426-29. A 5-HT system that is defective, either by virtue of hypoplasia[11] (or aplasia[12]) of the arcuate nuclei or by virtue of a

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[8] Arcuate nucleus of medulla oblongata is "one of the group of small, irregular areas of gray substance found on the ventromedial aspect of the pyramid of the medulla oblongata." *Dorland's*, 1295. Studies have shown that "in a subset of babies who had died of what appeared to be SIDS … the arcuate nucleus was either completely missing on both sides or was much smaller than comparable controls." Tr. 412-13.

[9] Kinney, H., et al., *The serotonergic anatomy of the developing human medulla oblongata: Implications for pediatric disorders of homeostasis*, J. Chem. Neuroanat., 2011; 41: 12-199 [hereinafter *Kinney 1*].

[10] Kinney, H., et al., *The Brainstem and Serotonin in the Sudden Infant Death Syndrome*, Annu. Rev. Pathol. Mech. Dis., 2009; 4: 517-50 [hereinafter *Kinney 2*].

[11] Hypoplasia is defined as "incomplete development or underdevelopment of an organ or tissue; it is less severe in degree than aplasia." *Dorland's*, 905.

[12] Aplasia is defined as "lack of development of an organ or tissue." *Dorland's*, 116.

related abnormality, is impaired in its ability to monitor carbon dioxide levels in the body. Tr. 429-30. Vaccines, Dr. Miller argued, may serve as an exogenous stressor[13] by depressing the activity of 5-HT neurons in an already defective system. Tr. 439. By prompting the activity of certain cytokines that are known to reduce the activity of serotonergic neurons – namely, IL-1, IL-6, and IL-2 – the vaccination, Dr. Miller theorized, prevents an already-defective system from stimulating respiration. Tr. 469-70.

At hearing, Dr. Miller explained why, according to the Kinney model and his own theory, cytokine activity induced by inflammation in the body's periphery would be capable of depressing arousal even in a dysfunctional 5-HT system. Tr. 405-11; *but see* Tr. 337-40 (Dr. McCusker, Respondent's expert, testifying that an infant's defective 5-HT system prevents the system from receiving signals from cytokines, and thereby prevents vaccination-induced cytokine activity from depressing the 5-HT system's arousal function); *see also* Pet. Ex. 25[14] (explaining how IL-1 inhibits the firing of serotonergic neurons). Dr. Miller explained that a dysfunctional 5-HT system as described by Dr. Kinney is not completely absent; rather, it is simply reduced in terms of neurons and functionality: "when … IL-1 gets into the nervous system to act on reducing 5-HT activity, in a normal child, that reduction will be inconsequential because there's plenty of 5-HT neurons there. But in a child with far fewer 5-HT neurons, that could then become critical." Tr. 406. Dr. Miller testified that he has never seen an autopsy which showed the complete absence of all 5-HT neurons from the medulla. *Id*. Even if the number of receptor molecules is so reduced that it can't sense carbon dioxide, "there's nothing to suggest that the individual receptor molecules are defective …. [i]t's a cellular level problem, not a membrane or a protein level problem." Tr. 408.

In support of his theory, Dr. Miller pointed to neuropathological evidence in the record; namely, L.J.'s autopsy slides. Tr. 411-12. The four slides reviewed by Dr. Miller contained a piece from two sides of one "level" of the medulla of L.J's brain. Tr. 421-25. Based on his review, Dr. Miller concluded that there was "hypoplasia and aplasia" of an arcuate nucleus in L.J.'s case. *Id*. However, when asked whether Dr. Kinney would be likely to concur with this pathological finding, Dr. Miller clarified that

> reporting as a pathologist, she would likely say that the evidence is inadequate because [the slides contain] only one level [of the medulla,] and she has written

[13] Dr. Miller acknowledged that Dr. Kinney has never described vaccines as a potential exogenous stressor in her model. Tr. 443.

[14] Brambilla, D., et al., *Interleukin-1 inhibits firing of serotonergic neurons in the dorsal raphe nucleus and enhances GABAergic inhibitory post-synaptic potentials*, Eur. J. Neuroscie, 2007; 26: 1862-69 [hereinafter *Brambilla*].

> extensively that one should serially block the medulla and put through all the levels. She's described very carefully that …. One can see almost no arcuate nucleus and then at another level see a perfectly adequate one.

Tr. 450. In light of the fact that he was unable to review "all the levels of the medulla," Dr. Miller testified that he was unable to "diagnose," or to make a "pathological finding," that L.J. had a defective arcuate nucleus; rather, he found only a "reasonable probability" that her arcuate nuclei were defective. Tr. 450-51. He also testified that his findings regarding L.J.'s arcuate nucleus are "well short of diagnostic or even more probable than not." Tr. 463. He reiterated, however, that regardless of the deficiencies inherent in the slides, he would argue in favor of vaccine causation because, whether or not L.J.'s arcuate nuclei were compromised, she likely had "a defective brainstem serotonergic system." Tr. 482-83, 463, *Kinney 2* (concluding that 70% of cases thoroughly studied have a defect in the 5-HT system).

Dr. Miller conceded that several of Dr. Kinney's identified exogenous stressors may have been at play in L.J.'s case. He agreed that the autopsy findings suggest that L.J. "was at least partially on her right side" at the time of death, though he also opined that it is impossible to know in "what position she really was lying." Tr. 476-77. He also acknowledged that L.J. was potentially subject to an excessively warm sleeping environment because she was swaddled and wrapped in an additional blanket. Tr. 479, 481. He argued, however, that these factors are not as likely to have constituted the sole exogenous stressors – to the exclusion of vaccine-induced cytokine activity – in L.J.'s case. Tr. 483-84. Dr. Miller testified that the other potentially relevant exogenous factors 1) are "not backed by very much in the way of statistically valid evidence or epidemiology, but more by anecdote," and 2) "didn't strike [him] as significant" in L.J.'s case. Tr. 483-84. Dr. Miller did not rule out the possibility that, if other exogenous stressors were at play in L.J.'s case, they worked "synergistically" with vaccine-induced cytokine activity to cause her SIDS. Tr. 484.

Mr. Miller agreed that there is a dearth of epidemiology conclusively establishing a relationship between vaccination and SIDS. Tr. 439-40. He explained this phenomenon by pointing out that, although the population of vaccinated infants is very large, the percentage of that population that is neuropathologically vulnerable is very small.[15] Tr. 439-40. Dr. Miller pointed out that there is literature in support of his argument that specific cytokines are capable of impacting the 5-HT system, that the identified cytokines have been found in the serotonergic system of the medulla in SIDS cases, and that multiple stressors may work synergistically to cause SIDS. Tr. 486-91; *see also Brambilla*, *Rognum*. Addressing the *Vennemann* article, which

[15] Dr. Miller did not explain why this fact – i.e., the fact that the population of identified neuropathologically vulnerable infants is small – does not undermine Dr. Kinney's theory that neuropathological defects are a risk factor for SIDS. The population was large enough for Dr. Kinney to identify a correlation on its basis.

reported on a large case control study from Germany that found no association between vaccination and SIDS, Dr. Miller argued that the "vulnerable" population had not been accurately identified, because autopsies were performed by forensic pathologists, not neuropathologists, and because the study does not explain exactly what was examined in subjects' brains. Tr. 440-41; Resp. Ex. E16[16]. Dr. Miller also argued that the *Vennemann* authors' scientific methodology was insufficiently rigorous. Tr. 441.

ii. Dr. James Oleske

1. Qualifications

Dr. Oleske graduated from New Jersey Medical School and received a Masters in Public Health from the Columbia University School of Public Health. Pet. Ex. 37; Tr. 12. After completing a fellowship in "allergy/ immunology/ infectious disease," Dr. Oleske became a faculty member at the New Jersey Medical School, where he is currently the Director of the Division of Pediatric Allergy, Immunology, and Infectious Diseases. Tr. 13. Dr. Oleske has conducted extensive research on the immune system and immune responses, and is board certified in pediatrics, allergy, immunology, pediatric infectious diseases, and pediatric palliative end-of-life care. Tr. 15-16.

At hearing, the undersigned admitted Dr. Oleske as an expert in allergy, immunology, and infectious disease. Tr. 18.

2. Theory

Dr. Oleske, like Dr. Miller, has incorporated Dr. Kinney's Triple Risk Model in to his theory of causation. Pet. Ex. 36 at 2; Tr. 53-57. Dr. Oleske explained that, according to Dr. Kinney's model, "extrinsic and intrinsic risk factors converge" to prevent infants' brains from being able to "adequately control postnatal homeostasis," resulting in SIDS death. *Id*. According to his theory, the minor infection caused by vaccination – which he also refers to as an "inflammatory process"[17] – may function as the "exogenous stressor" in Dr. Kinney's model. Tr. 49-50, 52-53 (L.J.'s SIDS "more likely than not" resulted from an inflammatory response,

[16] Vennemann, M., et al., *Sudden infant death syndrome: no increased risk after immunization*, Vaccine, 2007; 25(2): 336-40 [hereinafter *Vennemann*].

[17] Dr. Oleske testified that, in the relevant medical literature, there is no significant difference between a "mild infection" and an "inflammatory process." Tr. 50. Similarly, the immune system "doesn't differentiate well between artificial infection immunization versus natural infection." Tr. 72-73.

and not from an alternate risk factor such as sleep position or excessive blankets); Pet. Ex. 24[18] at 1.

More specifically, Dr. Oleske opined that vaccinations produce an "intense local response" at the site of injection which, by design, becomes systemic. Tr. 22; 70-71 ("the inflammatory system that may be initiated by a local infection … soon becomes involved with the central nervous system or other systemic functions," such as brain function). "[T]he systemic system is … associated with a rich interaction with the central nervous system," making "the brain and the peripheral immune systems … intimately involved." Tr. 24-25. The vaccine's antigens are designed to "stimulate what's called T cell responses, which are those responses that can result in … the long-term protection from anything that happens with infections." Tr. 24.

Vaccinations are capable of functioning as "exogenous stressors" when vaccine-induced cytokine activity reaches the arousal center of an infant's brain. Tr. 50-51 (Dr. Oleske testifying that vaccination causes the release of cytokines, both locally and systemically, and that vaccination always results in an inflammatory response, even in the absence of outward clinical symptoms); Pet. Ex. 36 at 2 ("[i]n this model, there is support for the role of cytokines as mediators for such failures of respiratory/ arousal functions in a susceptible infant during this window of vulnerability."). Especially in conjunction with adjuvants,[19] vaccinations increase the presence of the pro-inflammatory cytokines IL-1, IL-2, and IL-6 in the caudal serotonergic area of the infant's brain, which inhibits the effect of the 5-HT neurons, whose function is to mediate the arousal response. Pet. Ex. 36 at 3-4; Tr. 71-72 (describing the role of the 5-HT system in "control[ling] extreme variations in temperature and respirations and vital signs and vital status"), 77 (describing the 5-HT system as playing an important role in homeostasis); Tr. 125 (opining that the immunizations "impaired" and "overwhelmed" L.H.'s 5-HT system). *See also Brambilla* (explaining that IL-1, an inflammatory mediator, inhibits the firing of 5-HT neurons); Tr. 85-86.

Dr. Oleske pointed to epidemiological evidence in support of his testimony regarding the impact of cytokine activity on the 5-HT system. At least one study has found relatively high levels of the cytokine IL-1B in the brains of SIDS victims. *Kadhim 1* at 1 (finding high levels of IL-1B in the arcuate nuclei of 17 out of 17 studied SIDS victims, but in only one of six non-SIDS

[18] Kadhim, H., et al., *Distinct cytokine profile in SIDS brain: A common denominator in a multifactorial syndrome?*, Neurology, 2003; 61: 1256-59 [hereinafter *Kadhim 1*].

[19] Dr. Oleske testified that the DTaP and Prevnar vaccines contain "alum-type" adjuvants. Tr. 20. Aluminum adjuvants are "an aluminum-containing compound … that by combining with soluble antigen forms a precipitate; slow release of the antigen from the precipitate on injection causes prolonged, strong antibody response." *Dorland's*, 32.

brains); Tr. 81-82. Another study has found that IL-6 is elevated in the cerebrospinal fluid ("CSF") of SIDS victims. Pet. Ex. 26.[20] A third study has shown that IL-6 plays a role in communication between the peripheral nervous system and the brain. *See* Pet. Ex. 29[21] at 3, 7 (noting that "arousal from quiet sleep is impaired following infection and … this could explain increased risk for SIDS following infection, as shown in many studies," and that IL-6 levels were increased in the CNS of patients who had died of SIDS); Tr. 91-92. According to animal models, the cytokine IL-B, when injected, can cause apnea and repression of respiration. Pet. Ex. 22[22], 23[23]; *see also* Tr. 79-80. Dr. Oleske argued that several studies have shown a statistically significant increase in risk for SIDS death following administration of hexavalent vaccinations. *See* Pet. Ex. 31[24] (finding a 13-fold increase in risk); Pet. Ex. 33[25] (finding increased risk between zero and seven days post-vaccination).

In some infants, "there's a [pre-existing] defect in the 5-HT system, making them more susceptible to adverse events." Tr. 72. Normally, when an infant stops breathing, compensatory mechanisms in the infant's brain prompt the respiratory system to resume function. Pet. Ex. 36 at 2. When an "'at risk' infant stops breathing[,] a disturbance in the usual balance of cytokine activity in the arcuate nucleus blocks rather than stimulates a normal arousal signal, and the infant continues not to breath [sic], suffocates and dies (SIDS)." *Id*., Tr. 192-93; *Kinney 2*.

Dr. Oleske argued that the exogenous stressors at play in the Triple Risk Theory need not be limited to the mechanistic obstacles to respiration, such as upper respiratory infections ("URIs"), that were specifically identified by Dr. Kinney; in Dr. Oleske's view, other types of mild infections may, by virtue of the cytokine activity they prompt, also function as exogenous

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[20] Rognum, IJ., et al., *Interleukin-6 and the serotonergic system of the medulla oblongata in the sudden infant death syndrome*, Acta Neuropathol., 2009; 118: 519-30 [hereinafter *Rognum*].

[21] Vege, A., & Rognum, T., *Sudden infant death syndrome, infection and inflammatory responses*, FEMS Immunol. Med. Microbiol., 2004; 42: 3-10 [hereinafter *Vege*].

[22] Stoltenberg, L., et al., *Changes in apnea and autorescuscitation in piglets after intravenous and intrathecal interleukin-1â injection*, J. Perinat. Med., 1994; 22: 421-32.

[23] Froen, JF., et al., *Adverse effects of nicotine and Interleukin-1 on auto resuscitation after apnea in piglets: implications for sudden infant death syndrome*, Pediatrics, 2000; 105(4): 1-5.

[24] Zinka, B., et al., *Unexplained cases of sudden infant death syndrome shortly after hexavalent vaccination*, Vaccine, 2006; 24: 5779-80 [hereinafter *Zinka*].

[25] Traversa, G., et al., *Sudden unexpected deaths and vaccinations during the First Two Years of Life in Italy: a Case Series Study*, PLoS ONE, 2011; 6(1)(e16363): 1-10 [hereinafter *Traversa*].

stressors. Tr. 34-35. In support of this proposition, Dr. Oleske cited *Rognum*, according to which 40 percent of SIDS have been associated with "minor infection cases [with] a history of 'colds' or fever around the time of death." Tr. 36-46; *Rognum*. According to *Rognum*,

> Mild infection, especially in combination with prone sleeping condition, may be important exogenous triggers. In this regard, mild infection increases risk 1.7-fold, prone position 10.4-fold, and the two in combination, 29-fold. Now, by initiating a cytokine cascade, mild infection may trigger sudden death in an infant with an underlying pathophysiological process in the brainstem.

Rognum at 520 (noting also that there was an increase in IL-6 in the brains of infants who had died of SIDS); Tr. 87-88. *See also* Pet. Ex. 27[26] (noting that SIDS victims often have preceding mild infection/ inflammatory conditions).

Dr. Oleske has identified evidence in L.J.'s case that her vaccinations[27] were causally related to her death. He agrees that her death resulted from SIDS. Tr. 62-63. He testified that L.J. was healthy prior to her vaccinations, but that she was "somewhat irritable and ate less and was fussy" afterwards, at bedtime on the day of vaccination. Tr. 20; 206 ("I wouldn't term L.J.'s reaction 'extreme.' I think she was symptomatic, though, and had evidence of a reaction to the immunization."). He believes that L.J. was "in the appropriate sleeping position" on the night of her death, that there is no evidence to suggest that she was overheated or smothered. Tr. 115-16; 165 (noting that the police found L.J. "face-up"); 169 (testifying that, while they are exogenous factors identified by Dr. Kinney, there was no evidence that either the blanket or the swaddle put L.J. at risk). Dr. Olekse testified that, in infants, irritability and decreased appetite – both of which L.J. exhibited post-vaccination – may be evidence of sickness behavior. Tr. 28, 30, 33. He testified that, although there is no evidence in the record that L.J. had a fever post-vaccination, Mrs. Jewell did not take her temperature, and it is possible that L.J. had a fever that was not noticed by her parents. Tr. 21, 28. Indeed, it is difficult to determine whether any infant has a fever unless her temperature can be taken with a rectal thermometer; one can't necessarily tell from touching an infant that a fever is present. Tr. 28-29. Moreover, Dr. Oleske testified, L.J. may have had an "inapparent infection," in which case she appeared perfectly normal despite the fact that an inflammatory process was occurring inside her; "there's not always a

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[26] Kadhim, H., et al., *Interleukin-2 as a neuromodulator possibly implicated in the physiopathology of sudden infant death syndrome*, Neuroscience Letters, 2010; 480: 122-26 [hereinafter *Kadhim 2*].

[27] Dr. Oleske did not identify one or more of the administered vaccines as causal, but he did testify that the fact that L.J. received six vaccines at once makes their causative role more likely. Tr. 124 ("I would not have rated the one immunization to be as impacting as the combination.").

direct correlation between the level of the inflammatory responses and the symptoms that you exhibit." Tr. 66-67.

Dr. Oleske also believes that L.J. had an "underlying susceptibility" to SIDS, though he did not point to any biological evidence of this susceptibility in her case. Tr. 73-74; 104-106; 114; 150 (acknowledging a lack of neuropathological expertise, and testifying that he accepted Dr. Miller's assertion that L.J. had a brainstem abnormality). Even if L.J. did not have an identifiable brain abnormality, Dr. Oleske's theory would be that her vaccinations caused cytokine activity which impacted her brain and caused her death. Tr. 108-09; 163-64 (immaturity in the 5-HT may be to blame for an increased SIDS risk, even in the absence of structural abnormality). "[I]n a two-month old, what looks like a normal system is in a stage of development where it can be very overwhelmed … and you don't have to have [an identified defect]". Tr. 181.

Finally, Dr. Oleske testified that L.J.'s death occurred 10 to 15 hours post-vaccination, and that this onset period was temporally appropriate in light of the nature of L.J.'s inflammatory response. Tr. 57-58. L.J.'s immunological response went from local to systemic "within hours." Tr. 132-33.

Dr. Oleske conceded that, other than the petechiae found in L.J.'s lungs, there was no evidence of inflammation in L.J.'s case.[28] Tr. 135-36. He argued, however, that he would not have expected to see any such evidence, because the inflammation caused by the vaccinations would have occurred on a "microscopic," "cellular" level. *Id*. Dr. Oleske also conceded that, when cytokines are found in the brain, they are not necessarily evidence of an inflammatory response; cytokines are released "every second of every day," regardless of inflammation. Tr. 137. Moreover, Dr. Oleske conceded that, in some circumstances and in the right amounts, the release of cytokines may improve, rather than depress, respiratory responses. Tr. 141-42. Although "brain cytokines are neuroprotective when they are functioning under normal circumstances," they can become neurodamaging in the context of a "perfect storm" for SIDS. Pet. Ex. 36 at 4; Tr. 82 (one role of cytokines is to exert neuromodulatory effects).

Finally, Dr. Oleske testified that he is not surprised by the studies, identified by Respondent, which have concluded that there is no connection between administration of a hexavalent vaccine and an increased risk of sudden infant death. Tr. 161-62; *see also* Pet. Ex.

[28] Dr. Oleske later testified that petechiae occurs in almost every death; it is a post-mortem, not pre-mortem, effect. Tr. 173.

30[29], 31[30] (examining sample sizes of 420 and 6, respectively, and finding no link between vaccination and SIDS). According to Dr. Oleske, it would take a much larger study to identify any statistically significant increase in risk. Tr. 161-62.

b. Respondent's Arguments

i. Dr. Lucy Rorke-Adams

1. Qualifications

At the time of hearing, Dr. Rorke-Adams had been a specialist in pediatric neuropathology for 52 years and had been responsible for postmortem evaluation of central nervous system disease of at least 10,000 infants/children. Resp't's Ex. A at 1. She is currently board certified in anatomical pathology and neuropathology, is a reviewer and editor of various neurology and pathology journals, and is the namesake for a $2 million endowment for research on developmental neuropathology. Tr. 501-03.

At hearing, Dr. Rorke-Adams was admitted as an expert in pediatric neuropathology. Tr. 504.

2. Theory

Dr. Rorke-Adams testified that, in her view, and for two reasons, there was no relationship between L.J.'s vaccination and her death: first, because "[t]here's no evidence that the vaccination produced any change … [in L.J.'s] clinical presentation in the hours after the vaccination;" and second, because there was no "evidence in the postmortem examination of any change to the nervous system that might be attributed to some kind of effect from the vaccinations." Tr. 504-05.

Dr. Rorke-Adams disagreed with Dr. Miller's assessment of the pathological evidence and argued, in light of the limited nature of the samples, that the medulla slides "were not suspicious for" any defect of the arcuate nucleus or 5-HT system. Tr. 509-10. She explained that, having "looked at about 10,000 brains of infants and about 15,000 in adults over the span of [her] career, it is not uncommon to have a random selection of medulla in which you do not find

[29] Kries, R., et al., *Sudden and unexpected deaths after the administration of hexavalent vaccines (diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, Haemophilius influenzae type b): is there a signal?*, Eur. J. Pediatr., 2006; 164: 61-69.

[30] Zinka, B., *Unexplained cases of sudden infant death syndrome shortly after hexavalent vaccination*, Vaccine, 2005; 24: 5,779-80.

… neurons comprising the arcuate nucleus on either side." *Id*. Dr. Rorke-Adams also disagreed with Dr. Oleske's argument that the petechiae found in L.J. was evidence of inflammation; petechial hemorrhages are "a very characteristic feature of babies who die suddenly," regardless of the cause of death. Tr. 507-08. Dr. Rorke-Adams did agree that L.J. had been "bundled" in a way that may have implicated one of Dr. Kinney's risk factors, and that L.J.'s lividity may have suggested that she was on her side when she died. Tr. 516-17.

Finally, Dr. Rorke-Adams was reserved about the extent to which Dr. Kinney's Triple-Hit theory should be relied upon to explain what happened in L.J.'s case. She questioned Dr. Kinney's decision not to test for metabolic abnormalities in the studied SIDS population, noting that several studies have identified such abnormalities as an alternative cause of death in about 10% of infant deaths previously attributed to SIDS. Tr. 506-07. Dr. Rorke-Adams also questioned Dr. Kinney's inclusion of co-sleeping infants in the studied SIDS population because, she argued, SIDS is a diagnosis of exclusion, and because she believes that "co-sleeping" (also known as rollovers, layovers, and smothering) should be considered its own, independent cause of death. Tr. 513-17. Ultimately, Dr. Rorke-Adams believes that the Triple-Hit theory is a "hypothesis that needs to be proven;" and she does not personally believe that hypoplasia of the arcuate nucleus is a risk factor for SIDS. Tr. 524, 527.

ii. Dr. Christine C. McCusker

1. Qualifications

Dr. Christine McCusker graduated from McMaster University in Hamilton, Ontario, with a Master of Science (MSc) from the Department of Medical Sciences. Resp't's Ex. D. She subsequently received her MD from McMaster University Medical School and did her residency training in pediatrics at Montreal Children's Hospital, McGill University. *Id*. She completed clinical fellowship in allergy and immunology at McGill University in Montreal, Quebec. *Id*. At the time of hearing, Dr. McCusker was an associate professor of pediatrics at McGill University in Montreal. Tr. 212.

At hearing, the undersigned admitted her as an expert in pediatric immunology and clinical allergy and immunology. Tr. 215.

2. Theory

Dr. McCusker agreed with Petitioners' experts that infants of a certain age are particularly susceptible to SIDS because of the "maturation of the sleep arousal center in the CNS," and that deficits of medullary 5-HT system "have been implicated in abnormalities in respiration, arousal and chemoreception." Tr. 222, 344-46. However, Dr. McCusker disagreed

with Petitioners' experts regarding the likelihood that the vaccinations played a causal role in L.J.'s SIDS death via a systemic immune response. Although she acknowledged that cytokines may play a role in the brain's arousal activities, she disagrees that "cytokine activation secondary to vaccination [may play a role] in this process." Resp. Ex. F at 3. One reason for her opinion is that the cytokine activity triggered by vaccines is likely to be relatively controlled. "[C]ytokines by their very nature generally act over very short distances. They do not have very long half-lives, so they are rapidly degraded by the system;" "the vast majority of our inflammatory immune responses are sufficient at the local site to contain – control the infection, that you never actually know or see the immune response going on anywhere else." Tr. 221, 224. Adjuvants, which were present in the vaccines administered to L.J. for the purpose of augmenting her inflammatory response, have the effect of, "maintain[ing] the immune response relatively localized so that there are less systemic events." Tr. 278-79. Although vaccines do not always produce localized cytokine activity, it is often local, and it is almost always "well-controlled." Tr. 222, 308-09, 344-46. Infants' immune responses to vaccination, in particular, are likely to be local: "the infant immune system relies a lot more on … local responses, so that the receptors, the responsive elements for danger signals are differently regulated … so that the trigger or default pathway is to respond and contain in an infant." Tr. 227, 222, 344-46 (testifying that an infant's immune response to infection is "qualitatively and quantitatively" different from the infant's response to vaccination).

Dr. McCusker also testified that it is problematic, under Petitioners' theory of causation, that L.J. was afebrile after vaccination. Subjects with systemic cytokine activity are usually febrile. Tr. 221. When cytokines produce a systemic response, it is because they are communicating with each other to amplify the immune system's response, via a cascade effect; when sickness behavior occurs, it is because cytokines are upregulated, either peripherally or in the CNS. Tr. 221, 327-29. Fever is produced by the cytokines IL-6, TNF-alpha, and IL-1B via "signal transduction, through the combination of passage of the signal up the line … to the hypothalamus in the brain, … [where] they affect temperature regulation … in the interior pituitary." Tr. 221-22, 247-48. Vaccine-induced systemic cytokine activity capable of affecting the 5-HT system would also be likely to trigger the brain's fever response. Tr. 255 ("if you're talking about the mechanism by which it's the peripheral immune response that's activating the cytokine response in the CNS, you would expect the pathway to lead to fever"); *see also* Tr. 469-70 (Dr. Miller testifying that vaccination prompts systemic upregulation of IL-1, IL-6, and IL-2, which may prevent an already-defective 5-HT system from stimulating respiration), Pet. Ex. 36 at 3-4 (Dr. Oleske opining that, especially in conjunction with adjuvants, vaccinations increase the presence of the pro-inflammatory cytokines IL-1, IL-2, and IL-6 in the caudal serotonergic area of the infant's brain). Moreover, the cytokine activity that produces fever is designed to increase, not decrease, arousal. Tr. 255, 281; *but see Zinka*, *Traversa* (concluding, on the basis of animal models, that the cytokine IL-B, when injected, can cause apnea and repression of respiration).

Dr. McCusker specifically disagrees that vaccination-induced cytokine activity could serve as an "exogenous stressor" in Dr. Kinney's model. Tr. 241-42; 300 (describing Dr. Kinney's model as "a reasonable hypothesis"). She argues that vaccinations were not contemplated by Dr. Kinney as a potential exogenous stressor and would be an improper and unwarranted extension of Dr. Kinney's theory. Tr. 241-42; *Kinney 1* (identifying the exogenous stressors as sleep position, excessive bundling, soft bedding, and mild URIs). Unlike Dr. Kinney's exogenous stressors, which are all mechanical in that they mechanically obstruct respiration, vaccinations' alleged affect on respiration is neurochemical. Tr. 270-75. Adding a neurochemical stressor to a list of mechanical stressors would be like comparing apples to oranges. Tr. 275.

Generally speaking, Dr. McCusker testified, no conclusions regarding the causative role of vaccine-induced inflammation can be drawn on the basis of the presence of cytokines in the brain or CNS, because these cytokines are often present for reasons unrelated to inflammation. Tr. 302-05 (testifying that the presence of cytokines plays no causative or etiologic role in SIDS). Dr. McCusker explained that certain cytokines, such as IL-6, may be found in the brains of SIDS victims because "stress itself might signal to increase the IL-6 as a compensatory mechanism." Tr. 237-38. Another explanation for the increased presence of cytokines in the brains of SIDS victims is that they are the result of the body's attempt to compensate for malformed or immature 5-HT systems; the brain releases such cytokines when it wants to signal to the respiratory center that it needs to breathe. Tr. 242-44. In cases in which infants die of SIDS, the 5-HT system has ultimately failed to respond to this compensation attempt, but the cytokine increase is apparent in autopsy specimens. Tr. 244.

Even if cytokines were capable of suppressing the respiratory response in a normal brain, they would be incapable of doing so in a brain with a defective 5-HT system. The presence of inflammation or vaccination-induced IL-1 in a 5-HT system with a "developmental abnormality" would not be capable of inhibiting the firing of 5-HT neurons and thereby increasing respiration, as it would normally do, because the damaged 5-HT system is not capable of responding. Tr. 337-40 (analogizing the interaction to a defective door: "if the cytokine is knocking at the door … and the lock doesn't fit, the door doesn't work, the door won't open because the 5-HT is damaged"); *see also* Resp. Ex. E7[31] (explaining how IL-1B impacts the arousal center of the brain and may increase, rather than decrease, arousal).

Indeed, Dr. McCusker testified, "the global literature suggests that there is no association between vaccination and sudden infant death in large population trials." Tr. 259-64; *see also*

[31] Imeri, L. & Opp, M., *How (and why) the immune system makes us sleep*, Nat. Rev. NeuroSci, 2009; 10: 199-210.

Vennemann (finding, in a large case control study from Germany that was conducted as a follow up to the *Zinka* study, that here was no association between vaccination and SIDS[32]). She disagreed with Dr. Miller's assertion that epidemiological studies "not grounded in a through neuropathological examination" would be likely to identify a causal relationship in SIDS victims with pre-existing brainstem abnormality. Tr. 261-62 (testifying that "[w]ell-designed epidemiology is looking for the rare event as opposed to the common event"). Addressing the *Kinney 2* article, the conclusion of which was that medullary 5-HT defects are found in approximately 70% of SIDS deaths, she argued that "the references don't all have controls" and that there was an insufficient sample size. Tr. 341-42.

Dr. McCusker testified that there was no evidence in L.J.'s case that her immune system was compromised. Tr. 228. Although she conceded that L.J. may have experienced a mild infection or a mild immune response without fever, she argued that the absence of fever in L.J.'s case indicates that "there wasn't a huge immune response going on;" that "what was happening was not massive and overwhelming and particularly overwhelming from a CNS point of view." Tr. 252, 316. Dr. McCusker testified that L.J.'s symptoms of irritability and lack of appetite were mild, non-specific, and potentially unrelated to sickness behavior. Tr. 253-54, 316-320. There was no evidence, in Dr. McCusker's opinion, of any systemic cytokine activity on the day of L.J.'s death. Tr. 266.

Dr. McCusker identified several alternate extrinsic factors that qualify under Dr. Kinney's theory as "exogenous stressors" in L.J.'s case, and that may have played a causative role, independent of any vaccine-induced cytokine activity, in her death. The facts that L.J. was found by her mother with purple mottling of the right cheek and hand, and that she was on her right side, suggest that she was side-sleeping on the night she died. Tr. 257. "Side sleeping," as well as "prone position," are risk factors for SIDS. Tr. 258-59; *see also* Resp. Ex. E-10 (identifying risk factors that include bed sharing, prone or side sleeping, overbundling, soft bedding, face covered, and recent history of URI; and finding that 99% of SIDS infants had at least one risk factor for SIDS identified at the time of death).[33] Additionally, when law enforcement and emergency personnel responded to the scene of her death, L.J. was "bundled" and "had a blanket on top of her." Tr. 257-58.

[32] It is unclear to the undersigned whether the results of this study are statistically valid. *See* Tr. 377-87.

[33] Trachtenberg, F., et al., *Risk factor changes for sudden infant death syndrome after initiation of Back-to-Sleep campaign*, Pediatrics, 2012; 129: 630-38.

IV. ANALYSIS

A. *Althen* Prong 1

Under the first prong of *Althen*, Petitioners are required to set forth a medical theory that explains how the vaccinations can cause SIDS. *Althen*, 418 F.3d at 1278. The proffered "reputable" explanation must be scientifically "sound" and "reliable." *See Moberly*, 592 F.3d at 1325; *Althen*, 418 F.3d at 1278; *see also Knudsen*, 35 F.3d at 548 (Fed. Cir. 1994) (a causation theory before a special master must be supported by a "sound and reliable" medical or scientific explanation). Furthermore, "[a]ssessments as to the reliability of expert testimony often turn on credibility determinations, particularly in cases . . . where there is little supporting evidence for the expert's opinion." *Moberly*, 592 F.3d at 1325-26.

Applying this standard to the instant case, the undersigned acknowledges Dr. Kinney's Triple Hit Theory as a hypothetical model for factors relevant to the pathogenesis of SIDS. The undersigned finds the theory credible, and adopts it as an analytical framework for assessing Petitioner's theory of causation. However, the undersigned also finds that there is insufficient evidence in the record to support Petitioner's argument that vaccines should be included among Dr. Kinney's "exogenous stressors" as a potential causal factor in the pathogenesis of SIDS. The undersigned agrees with Respondent's experts that the common thread among Dr. Kinney's acknowledged exogenous stressors is that they function as a mechanical obstruction to respiration, and that it would be an unwarranted extension of Dr. Kinney's theory to find that a neurochemical obstacle to respiration, such as vaccination-induced cytokine activity, is of the same type.

The undersigned also finds that Petitioners have failed to prove that cytokine activity is capable of impacting the brain's 5-HT system in the ways proposed by Petitioner's experts. The undersigned acknowledges the existence of animal studies in support of Petitioners' argument that injected IL-1B may prolong apnea, but finds that Petitioners have failed to prove that vaccinations are capable of producing such cytokine activity in the brain. *See Froen*, *Stoltenberg*

B. *Althen* Prong 2

Under the second prong of *Althen*, Petitioners are required to establish "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." Petitioners must also prove that the vaccine actually *did* cause the alleged injury in the instant case. *See Pafford*, 2004 WL 1717359, at *4; *Althen*, 418 F.3d at 1279.

As an initial matter, the undersigned finds that Petitioner has failed to prove that L.J. suffered from any brain defect, either in the form of aplasia or hypoplasia of the arcuate nucleus or in any other form. Dr. Oleske has conceded that he lacks the neuropathological expertise to opine regarding the existence of any defect, and Dr. Miller has conceded that his findings regarding L.J.'s arcuate nucleus are "well short of diagnostic or even more probable than not." Tr. 150, 463. Dr. Rorke-Adams testified that the neuropathological evidence in this case was not suspicious for any defect of the arcuate nucleus or of the 5-HT system. Tr. 509-10.

Assuming that L.J.'s failure to respond to arousal triggers resulted in part from an immature, though not defective, 5-HT system, the undersigned also finds that the lack of a documented fever in L.J.'s case makes it particularly unlikely that systemic cytokine activity was affecting her brain in the ways suggested by Petitioner's experts. The undersigned acknowledges Dr. Oleske's argument that L.J. may have had an unnoticed fever or an "inapparent infection," but is unable to find, in the absence of any affirmative evidence of the existence of an inflammatory process in L.J.'s case, that systemic cytokine activity was occurring at the time of her death. *See* Tr. 28-29 (Dr. Oleske testifying about the difficulties inherent in taking an infant's temperature); 66-67 (Dr. Oleske testifying inflammatory responses are not always associated with symptoms); 221 (Dr. McCusker testifying that subjects with cytokine activity are usually febrile); 255 (Dr. McCusker testifying that vaccine-induced systemic cytokine activity capable of affecting the 5-HT system would also be likely to trigger the brain's fever response); 252, 316 (Dr. McCusker testifying that the absence of fever in L.J.'s case suggests that "there wasn't a huge immune response going on" and that "what was happening was not massive and overwhelming and particularly overwhelming from a CNS point of view"); 469-70 (Dr. Miller testifying that vaccination may prompt systemic upregulation of IL-6, which is one of the cytokines associated with fever production). The undersigned also finds that the petechiae found in L.J.'s lungs was more likely to have been a post-mortem effect than evidence of pre-mortem inflammation. *See* Tr. 173 (Dr. Oleske testifying that there is evidence of petechiae in almost every death), 507-08 (Dr. Rorke-Adams testifying that petechial hemorrhages are "a very characteristic feature of babies who die suddenly," regardless of the cause of death).

Moreover, the undersigned finds that there were exogenous factors at play in L.J.'s case, factors recognized by Dr. Kinney as potentially causative, that these factors were potential contributors to L.J.'s death, and that these factors would have functioned independently of the alleged neurochemical causes. Dr. Miller has conceded that several other of Dr. Kinney's identified exogenous stressors may have been at play in L.J.'s case. Tr. 476-77 (agreeing that L.J. may have been "partially on her right side" at the time of death), 479, 481 (agreeing that she was potentially subject to hyperthermia and swaddling). The undersigned acknowledges that multiple stressors create a higher SIDS risk and that such stressors may work "synergistically," but finds that Petitioners have failed to prove that this synergistic effect was more likely to have been caused by neurochemical stressors than it was to have been caused by the Kinney-identified

stressors that were objectively observable in L.J.'s case. *See Zinka* (noting a 13-fold increase in risk in cases involving multiple risk factors); Tr. 484 (Dr. Miller opining that stressors may work synergistically).

C. *Althen* Prong 3

If Petitioners' cytokine theory were viable, the undersigned would find that L.J.'s death was temporally proximate, under that theory, to the administration of the vaccines. However, in light of the undersigned's findings on *Althen*'s first and second prongs, this proximity does not advance Petitioners' claims under *Althen*.

V. CONCLUSION

The undersigned is sympathetic to the fact that Petitioners lost their child to SIDS. However, the undersigned finds that Petitioners have failed to prove, by a preponderance of the evidence, that L.J.'s vaccinations caused her SIDS. Therefore, the undersigned has no choice but to DENY Petitioners' claim and DISMISS this petition.

In the absence of a motion for review filed pursuant to RCFC Appendix B, the clerk of the court **SHALL ENTER JUDGMENT** accordingly.

IT IS SO ORDERED.

/s/ Lisa D. Hamilton-Fieldman
Lisa D. Hamilton-Fieldman
Special Master